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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,133	12/15/1999	ELISABETTA VEGETO	246/180	8491

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LYON & LYON LLP
633 WEST FIFTH STREET
SUITE 4700
LOS ANGELES, CA 90071

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	15

DATE MAILED: 06/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/465,133	VEGETO ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on th c ver sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *100-105,107,108,111-123,127 and 129-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100-105,107,108,111-123,127 and 129-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 100-105, 107, 108, 111-123, 127 and 129-143 are pending in the application.

This Office Action is in responses to the Amendment filed on 3/14/02.

Response to Amendment

The rejection of claims 100-105, 107, 108, 111- 123, 127 and 129-143 under 35 U.S.C 112 second paragraph (lack essential elements) has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 100-105, 107, 108, 111- 123, 127 and 129-143 under 35 U.S.C 112 second paragraph (indefinite language) has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 100-105, 107, 108, 111-123, 127 and 129-143 under 35 U.S.C 112 first paragraph (enablement) has been changed to scope of enablement in light of Applicants' amendment of claims.

Claims 100-105, 107, 108, 111-123, 127 and 129-143 under stand rejected under 35 U.S.C 112 first paragraph (written description) for reasons made of record in the Office Action mailed on 8/31/01 and further discussed below.

Claims 100-105, 107, 108, 111-123, 127 and 129-143 are rejected under 35 U.S.C 101 for reasons set forth below.

Claims 111, 118, 119, 136, 137, 141-143 are rejected under 35 U.S.C 112 second for reasons set forth below.

Response to Arguments

In response to the rejection to claims 100-105, 107, 108, 111-123 and 129-143 under 35 U.S.C 112 first paragraph (written description), Applicants argue a) the specification has sufficiently and particularly disclosed species representative within the genus of "desired gene" or "desired protein," and the "phenotypic effect" is not a limitation of the claims; and b) the specification has provided structural elements that the claimed "mutated steroid hormone superfamily receptor ligand binding domain" must share and the method of obtaining those mutants, therefore, the written description requirement is satisfied.

The Examiner agrees with Applicants' first argument in regard to genus of "desired gene" or "desired protein", however, the second argument in regard to "mutated steroid hormone superfamily receptor ligand binding domain" is not convincing for the same reasons made of record in the prior Office Action and discussed here. Briefly, the claims encompass any and all mutations to steroid receptor ligand binding domains that are capable binding an antagonist (of the natural occurring binding domain) and causes transcription of the responsive gene. However, the specification only shows a single example of progesterone receptor with a deletion of 42 amino acid from C-terminus that is capable of binding RU38486, a natural antagonist of the progesterone receptor.

The state of art at the time of filing does not teach whether other types of mutations, such as sequence substitutions or additions, are capable of producing a mutant receptor that is capable of binding an natural antagonist, and whether deleting a 42 amino acid sequence from the C-terminus of other types of steroid receptor ligand binding domains would result in a mutant receptor with claimed characteristics. The specification also does not provide adequate

description of the common structural elements those mutations must share to produce a receptor with claimed characteristics. Therefore, the written description requirement is not satisfied.

In response to the rejection to claims 100-105, 107, 108, 111-123, and 129-143 under 35 U.S.C. 112 first paragraph (enablement), Applicants argue that the claims do not have a limitation requiring "phenotypic effects" of the transgenic animal. Applicants cite *Ex Parte* Chen and argue that the discussion of unpredictability of transgenic animal is inapplicable. Applicants further argue that the issue addressed by the rejection is whether the claimed invention is useful, and indicate that the specification supports the usefulness of the claimed molecular switch. Applicants also indicate that the invention encompass direct injection of the molecular switch/nucleic acid cassette into a target cell for in vivo gene therapy, and submitted a copy of the Declaration of Jeff Nordstrom to show that regulation of expression of SEAP in mice using the claimed invention. Applicants further argue that the breath of the claims does not include all mutations of the steroid hormone receptor family ligand binding domain, but only those that are capable of binding to a ligand that is an antagonist for the non-mutated receptor protein. Applicants conclude that such receptors can be screened by the routine method as disclosed in the specification.

In response to Applicants' arguments about "phenotypic effects," the Examiner agrees that the "phenotypic effects" is not a limitation of the claims, however, it is a required element for the enablement of the claims. The case law of *Ex Parte* Chen does not apply to the current case because the is not based on the argument that transgenic animals cannot be consistently made, but rather how to use the transgenic animals without any "phenotype," in the instant case, the expression of the protein or RNA. The method of regulating gene expression in vivo as

claimed encompasses the use of transgenic animal comprising a construct encoding the mutant receptor and another construct encoding the responsive element to the receptor and a reporter gene. However, as indicated in the previous Office action, it is unpredictable whether the transgene would be expressed at a level sufficient to cause a particular phenotype (see page 8-9 of the previous action for details). In other words, it is unpredictable whether the transgene would be expressed at a high enough level so that it can be detected, and thereby, the expression can be regulated. One skilled in the art would not know how to use transgenic animals that simply comprise the transgene without actual mRNA or protein expression to practice the method as claimed. Therefore, the method is not enabled because the essential element required to practice the method, the transgenic animal, is not enabled.

In response to Applicants' argument of direct injecting the nucleic acid construct to the animal, the Examiner considers the argument to be partially persuasive. The Declaration of Jeff Nordstrom has been considered and the Examiner agrees that the method is enabled for transient expression of both construct in a localized site in a mouse, however, the data is clouded by the fact that the "gene switches" used in the experiments (CMV-GS2.0 and CMV-GS3.1) are not supported by instant specification. It is not clear whether the "gene switches" disclosed in the declaration are the same mutant receptors disclosed in the specification (if it is, which one?) or there are additional modifications have been introduced in the Nordstrom laboratory. Nevertheless, the Examiner considers that the method is enabled for transient expression of both construct in a localized site in a mouse, however, the method is not enabled for regulating gene expression in any transgenic non-human animal (see reasons in the previous paragraph), and for long-term expression in vivo.

In response to Applicants' argument in regard to "mutated steroid hormone receptor superfamily ligand binding domain," the Examiner finds the argument not convincing. Although the breath of the claims include only "mutated steroid hormone receptor superfamily ligand binding domain that are capable of binding to a ligand that is an antagonist for the non-mutated receptor protein," the specification only disclose one working example of a mutated receptor of such kind. Based on the disclosure of the specification, whether mutations of other kind would produce a receptor having the characteristics as claimed is unpredictable, and whether deleting same number of amino acid from C-terminal of other receptors in the steroid hormone receptor superfamily would produce a receptor having the characteristics as claimed is also unpredictable. The specification only provides sufficient support for the enablement of the claimed method comprising a progesterone receptor with at least 42 C-terminal amino acid deletion having the claimed characteristics. In view of lack of teaching from the specification and art, one of skill in the art would have to engage in undue amount of experimentation to practice the method in commensurate in the scope of the invention. Applicant is advised to amend the claims so they only read on the invention that is considered enabled by the support of specification.

New Grounds of Rejection

Claims 118, 119, 136, 137, 142 and 143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 118 and 119, the term "transcription region" renders the claims indefinite because it is unclear what region Applicants are referring to. A transcription region is the part of DNA sequence that is transcribed into mRNA. However, it appears that Applicants are referring to a transactivation domain of a protein. Applicants need to amend the claims so they clearly read on the claimed subject matter.

Regarding claims 136 and 137, the word "derived" renders the claims indefinite because the nature and derivative process is unknown. As such, the metes and bounds of the claims cannot be established.

Claims 142 and 143 recite the limitation "regulated expression" in line 1. There is insufficient antecedent basis for this limitation in the claim.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claims 100-105, 107, 108, 111-123, 127 and 129-143 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating gene expression transiently in vivo by either a) introducing into a wild type animal a construct encoding a progesterone receptor with at least 42 amino acid deletion from C-terminal, and another construct comprising a progesterone receptor responsive element linked to a report gene; b) administering a ligand that binds to said mutated receptor to said animal, or administering a ligand that binds to a mutated steroid receptor to a transgenic non-human animal, wherein said transgenic non-human animal expresses a heterologous reporter gene and a mutated steroid receptor, wherein expression of said receptor regulates the expression of the reporter gene by

binding to the promoter of said reporter gene, does not reasonably provide enablement for said method utilizing any transgenic animal or long term expression in any animal, and/or any mutated steroid hormone receptor that is capable of binding ligand that is an antagonist of the natural occurring receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims (see the reasons discussed in the response to amendment section).

Claims 111, 139 and 141 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "molecular switch" renders the claims indefinite because it is unclear whether the "molecular switch" is a nucleic acid or a protein. Claim 1, the parent claim of claim 111, recites "molecular switch promoter." However, claim 135, the parent claim of claims 139 and 141, recites "molecular switch promoter." Applicant needs to use consistent terminology throughout the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 3, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600